

NIH Consensus Development Conference Statement on Inhaled Nitric Oxide Therapy for Premature Infants



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The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research, and that the information provided is not a substitute for professional medical care or advice.

Reference Information

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The evidence report prepared for this conference through AHRQ is available on the web via <http://www.ahrq.gov/clinic/tp/inoinftp.htm>. Printed copies may be ordered from the AHRQ Publications Clearinghouse by calling **800-358-9295**. Requesters should ask for AHRQ Publication No. **11-E001**.

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Disclosure Statement

All of the panelists who participated in this conference and contributed to the writing of this statement were identified as having no financial or scientific conflict of interest, and all signed forms attesting to this fact. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on NIH Consensus and State-of-the-Science Panels are reviewed prior to selection to ensure that they are not proponents of an advocacy position with regard to the topic and are not identified with research that could be used to answer the conference questions.

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Archived Conference Webcast

The NIH Consensus Development Conference: Inhaled Nitric Oxide Therapy for Premature Infants was webcast live October 27–29, 2010. The webcast is archived and available for viewing free of charge at ***<http://consensus.nih.gov/2010/ino.htm>***.

Abstract

Objective

To provide healthcare providers, patients, and the general public with a responsible assessment of currently available data on the use of inhaled nitric oxide in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation who require respiratory support.

Participants

A non-Department of Health and Human Services, nonadvocate 16-member panel representing the fields of neonatology, pediatric pulmonology, pediatric neurology, perinatal epidemiology, ethics, neurodevelopmental follow-up, nursing, and family-centered care. In addition, 18 experts from pertinent fields presented data to the panel and conference audience.

Evidence

Presentations by experts and a systematic review of the literature prepared by the Johns Hopkins University Evidence-based Practice Center, through the Agency for Healthcare Research and Quality (ARHQ). Scientific evidence was given precedence over anecdotal experience.

Conference Process

The panel drafted its statement based on scientific evidence presented in open forum and on published scientific literature. The draft statement was presented on the final day of the conference and circulated to the audience for comment. The panel released a revised statement later that day at <http://consensus.nih.gov>. This statement is an independent report of the panel and is not a policy statement of the National Institutes of Health (NIH) or the Federal Government.

Conclusions

(1) Taken as a whole, the available evidence does not support use of inhaled nitric oxide in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation who require respiratory support. (2) There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which inhaled nitric oxide may have benefit in infants <34 weeks gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties. (3) Basic research and animal studies have contributed to important understandings of inhaled nitric oxide benefits on lung development and function in infants at high risk of bronchopulmonary dysplasia. These promising results have only partly been realized in clinical trials of inhaled nitric oxide treatment in premature infants. Future research should seek to understand this gap. (4) Predefined subgroup and post hoc analyses of previous trials showing potential benefit of inhaled nitric oxide have generated hypotheses for future research for clinical trials. Prior strategies shown to be ineffective are discouraged unless new evidence emerges. The positive results of one multicenter trial, which was characterized by later timing, higher dose, and longer duration of treatment, require confirmation. Future trials should attempt to quantify the individual effects of each of these treatment-related variables (timing, dose, and duration), ideally by randomizing them separately. (5) Based on assessment of currently available data, hospitals, clinicians, and the pharmaceutical industry should avoid marketing inhaled nitric oxide for premature infants <34 weeks gestation.

Introduction

Premature birth is a major public health problem in the United States and internationally. Despite clinical, educational, and scientific efforts, the frequency of preterm birth has risen in the United States from 10.6 percent in 1990 to 12.7 percent in 2007. Worldwide, approximately 13 million infants are born prematurely every year. Infants born at or before 32 weeks gestation (2 percent of all births in the United States in 2007) are at extremely high risk for death in the neonatal period or for pulmonary, visual, and neurodevelopmental morbidities with lifelong consequences, including bronchopulmonary dysplasia (a form of chronic lung disease seen in premature infants), retinopathy of prematurity (the leading cause of blindness in children in the developed world), and brain injury. Reduced lung function associated with prematurity may persist throughout childhood and adolescence. Neurodevelopmental problems—including cerebral palsy, blindness, hearing loss, and learning disabilities—create lifelong challenges for many of these children and their families. Risks for adverse outcomes increase with decreasing gestational age. The economic costs to care for these infants are also substantial (estimated at \$26 billion in 2005 in the United States). In addition, the emotional and indirect economic costs for families are substantial. Unfortunately, however, the multifactorial biological, behavioral, and environmental causes and the heterogeneity of preterm birth make it extremely unlikely that all premature births can be prevented.

Over the past 20 years, continuing advances in high-risk obstetrical management and neonatal intensive care have resulted in increased survival of extremely premature infants. For example, based on recent Cochrane reviews, administration of antenatal steroids to women with impending premature birth reduces the risk of in-hospital neonatal death by 23 percent, neonatal respiratory distress syndrome by 34 percent, and cerebroventricular hemorrhage by 46 percent. Exogenous surfactant administered to premature infants to either treat or prevent

respiratory distress syndrome improves respiratory function and reduces risk of in-hospital death by 32 to 40 percent. After demonstration of efficacy and safety in multiple randomized controlled trials, both of these interventions have been adopted into clinical practice.

Many clinical practices integrated into the care of these infants have been inadequately studied for safety and efficacy, with potentially serious consequences; yet, the smallest and sickest infants are the most vulnerable to adverse effects of the treatments they receive. The broad boundaries of accepted clinical practices in neonatal intensive care units lead to practice variations among centers. Large variations among centers in outcomes of premature infants, including bronchopulmonary dysplasia and adverse neurodevelopmental outcomes, persist after adjusting for risk factors such as gestational age, sex, and disease severity. The extent to which these differences in outcomes are due to differences in care practices or in patient characteristics is poorly understood. Clearly, the need for strategies to improve outcomes for this high-risk population is great, and this need has prompted testing of new therapies with the potential to decrease pulmonary and other complications of prematurity. Inhaled nitric oxide emerged as one such therapy.

Nitric oxide is a gas that is ubiquitously produced in the human body. It serves as a signaling molecule with numerous regulatory effects on multiple human organ systems, including blood vessels, the lung, the heart, the nervous system, the immune system, and stem cells, and on the development of cancer. First discovered as a factor that relaxes resistance in blood vessels in 1980, nitric oxide was recognized by *Science* as the “Molecule of the Year” in 1992. The scientists who discovered its important role in diverse disease processes, including atherosclerosis, diabetes, impotence, and hypertension, were recognized with the Nobel Prize for Medicine or Physiology in 1998. More than 85,000 independent scientific articles about nitric oxide have been published

since 1980. Over the past decade, the efficacy of nitric oxide in reducing blood vessel resistance and its easy administration via endotracheal tube to infants with respiratory distress led to trials in term and near-term newborns suffering from persistent pulmonary hypertension, a condition that results from failure of normal fetal lung blood vessel relaxation immediately following birth. Prior to inhaled nitric oxide trials, many infants severely affected with pulmonary hypertension were treated using extracorporeal membrane oxygenation, an invasive heart-lung bypass system, as a short-term strategy (up to 14 days) to improve survival by “buying time” for lung blood vessel resistance to decrease spontaneously. Extracorporeal membrane oxygenation therapy is expensive, not widely available, and associated with considerable morbidity (e.g., bleeding). Large, placebo-controlled trials showed that nitric oxide decreases risk of death or the need for extracorporeal membrane oxygenation in term and near-term infants with persistent pulmonary hypertension and led the Food and Drug Administration to approve inhaled nitric oxide as a therapy for that disease.

Findings from a substantial body of experimental work in developing animals and other model systems suggest that nitric oxide may enhance lung growth and reduce lung inflammation independently of its effects on blood vessel resistance. Although this work demonstrates biologic plausibility and the results of randomized controlled trials in term and near-term infants were positive, combined evidence from the 14 randomized controlled trials of inhaled nitric oxide treatment in premature infants <34 weeks gestation have shown equivocal effects on pulmonary outcomes, survival, and neurodevelopmental outcomes. Despite these equivocal results, the off-label use of inhaled nitric oxide has increased substantially. Controversy about its use in premature infants has been fueled by the refusal of some third-party payers to cover the substantial costs for inhaled nitric oxide administration (up to \$3,000 a day).

To provide healthcare professionals, families, and the general public with a responsible assessment of currently available data regarding the benefits and risks of inhaled nitric oxide in premature infants, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Heart, Lung, and Blood Institute, and the Office of Medical Applications of Research of the National Institutes of Health convened a Consensus Development Panel that included experts in the fields of neonatology, pediatric pulmonology, pediatric neurology, perinatal epidemiology, ethics, neurodevelopmental follow-up, nursing, and family-centered care to review available data, to hear scientific summaries from investigators involved in this field, and to solicit input from the general public. A Planning Committee developed six questions to be addressed by the Consensus Development Panel.

As part of a comprehensive data review, an independent group, the Johns Hopkins University Evidence-based Practice Center, generated a systematic review of all available human studies concerning use of inhaled nitric oxide in premature infants. This review (available at <http://www.ahrq.gov/clinic/tp/inoinftp.htm>), along with an as yet unpublished, updated Cochrane review and an unpublished individual patient data meta-analysis (the Meta-Analysis of Preterm Patients on Inhaled Nitric Oxide [MAPPiNO] meta-analysis), provided the panel with summaries of the available evidence from these trials. One of the published trials, and therefore the Johns Hopkins University Evidence-based Practice Center systematic review, included infants of 34 weeks gestation. The panel's review of the published evidence is therefore based on infants ≤ 34 weeks gestation. Its recommendations for clinical use of inhaled nitric oxide, however, are limited to infants < 34 weeks to avoid contradiction and confusion with the Food and Drug Administration's labeled indications for inhaled nitric oxide use.

Combining results of studies is complicated by differences in dose, timing, and duration of inhaled nitric oxide administration, inclusion criteria (e.g., gestational age, chronologic age, severity of lung disease) of infants studied, and diversity of neurodevelopmental and pulmonary outcome measures. Where applicable, the panel chose to follow the Cochrane review approach of subdividing the 14 trials into 3 clinically relevant groups based on characteristics of the participating infants and specific treatment strategies: early routine (initiation at <3 days, routine use in intubated infants), early rescue (initiation at <3 days based on oxygenation status), and later rescue (initiation at >3 days based on bronchopulmonary dysplasia risk).

Many of the trials and meta-analyses examined results in clinical or demographic subgroups. When treatment effects differ across subgroups, however, as they did in some of the inhaled nitric oxide studies, it is unwise to make firm inferences about subgroup differences when those differences are observed post hoc. Post hoc analysis of treatment effects in specific subgroups (e.g., dose of inhaled nitric oxide, gestational age, early versus late initiation of treatment), whether within or across trials, is prone to false-positive results. The Consensus Development Panel therefore considered the subgroup results of these analyses as hypothesis-generating, rather than hypothesis-testing, and used them as a basis for recommending future research directions.

The six questions considered by the Consensus Development Panel are listed below and addressed in the following sections.

1. Does inhaled nitric oxide therapy increase survival and/or reduce the occurrence or severity of bronchopulmonary dysplasia among premature infants who receive respiratory support?

2. Are there short-term risks of inhaled nitric oxide therapy among premature infants who receive respiratory support?
3. Are there effects of inhaled nitric oxide therapy on long-term pulmonary and/or neurodevelopmental outcomes among premature infants who receive respiratory support?
4. Does the effect of inhaled nitric oxide therapy on bronchopulmonary dysplasia and/or death or neurodevelopmental impairment vary across subpopulations of premature infants?
5. Does the effect of inhaled nitric oxide therapy on bronchopulmonary dysplasia and/or death or neurodevelopmental impairment vary by timing of initiation, mode of delivery, dose and duration, or concurrent therapies?
6. What are the future research directions needed to better understand the risks, benefits, and alternatives to nitric oxide therapy for premature infants who receive respiratory support?

Terminology surrounding disease processes in premature infants has been used in inconsistent ways. For clarity throughout this document, the panel has chosen to define the following terms:

Premature infant: The International Classification of Diseases has eliminated the term “prematurity,” because its prior definition was based on birth weight. This term is commonly used and understood as a synonym for preterm birth, defined by the International Classification of Diseases as a gestational age at birth <37 completed weeks. Because the questions posed to the panel used *premature infant*, this term is used throughout this consensus statement as a synonym for preterm infant. In this document, “near-term” is used as it reflects the

specific language in the Food and Drug Administration-approved label for inhaled nitric oxide. The panel recognizes that “late preterm” is currently used to describe infants at 34 and up to 36 weeks and 6 days gestation.

Bronchopulmonary dysplasia: First described in 1967, bronchopulmonary dysplasia is a heterogeneous lung disease observed in premature infants and diagnosed within the first months of life. The clinical picture and definition of bronchopulmonary dysplasia have evolved substantially since its first description, complicating comparisons of studies that use bronchopulmonary dysplasia as an outcome. In analyzing the studies of inhaled nitric oxide discussed in this report, the panel decided to follow the definitions of bronchopulmonary dysplasia used by the researchers who designed the different clinical trials.

Cerebroventricular hemorrhage: This term is used as an inclusive term to refer to the spectrum of hemorrhagic brain injury most typically occurring in the first week of life in very premature infants. The location of hemorrhage may be periventricular, intraventricular, or intraparenchymal. Most studies report both the presence of any brain hemorrhage and severe hemorrhage. Severe hemorrhage most often refers to a large intraventricular hemorrhage or hemorrhage into white matter that surrounds the ventricles.

White matter injury: White matter injury is a spectrum of brain pathology that includes (1) the classic lesion of periventricular leukomalacia, which comprises focal cystic damage to white matter tracts (made of nerve axons that connect different brain regions covered by the insulating substance, myelin), and (2) diffuse, noncystic lesions that result in disturbances in myelination.

1. Does Inhaled Nitric Oxide Therapy Increase Survival and/or Reduce the Occurrence or Severity of Bronchopulmonary Dysplasia Among Premature Infants Who Receive Respiratory Support?

A body of evidence is strongest when results are consistent across trials despite heterogeneity in study design and populations. Therefore, the panel chose to address this question by including all of the trials that enrolled premature infants <34 weeks gestation irrespective of the timing, dosing regimen, duration of inhaled nitric oxide therapy, or subcategorization of the subjects.

None of the individual trials included in the systematic reviews showed a statistically significant effect of inhaled nitric oxide on survival in this population. Meta-analysis by the Johns Hopkins University Evidence-based Practice Center of 11 randomized controlled trials revealed that treatment with inhaled nitric oxide did not increase survival. The individual patient data approach used in the MAPPiNO study of pooled data from 11 randomized controlled trials demonstrated no statistically significant effect of inhaled nitric oxide on death at any time, death by 36 weeks postmenstrual age, or death before discharge. Given that the mortality of premature infants is highest during the first week after birth, age at the time of study enrollment is likely to be a particularly important factor in analyzing the effect of inhaled nitric oxide on survival. However, inclusion or exclusion of the one trial with enrollment exclusively after 1 week did not affect the results of the meta-analysis. Thus overall, in premature infants <34 weeks gestation requiring respiratory support, current evidence shows that treatment with inhaled nitric oxide in the neonatal period does not increase survival.

Bronchopulmonary dysplasia is defined in the Introduction. The evolution of bronchopulmonary dysplasia over decades has been reflected in numerous and various definitions, usually based on the persistence of respiratory symptoms, pulmonary radiographic appearance, and the persistent need for treatments at a specified age (e.g., requiring supplemental oxygen at 28 days of age, requiring supplemental oxygen at 36 weeks postmenstrual age).

Interpretation of results from randomized controlled trials was complicated by different studies calculating bronchopulmonary dysplasia rates using survivors versus the total group as the denominator, and by the competing risks of death and bronchopulmonary dysplasia. In other words, an infant who dies in the first weeks of life is not at risk for developing bronchopulmonary dysplasia, which is usually based on criteria at 28 days. Since most of the trials and the Johns Hopkins University Evidence-based Practice Center systematic review included analyses of bronchopulmonary dysplasia alone, however, the panel also examined that evidence. None of the individual trials included in the systematic reviews showed statistically significant differences in bronchopulmonary dysplasia at 36 weeks postmenstrual age in those who received inhaled nitric oxide compared with controls. The Johns Hopkins University Evidence-based Practice Center meta-analysis (8 randomized controlled trials) of bronchopulmonary dysplasia among surviving infants at 36 weeks postmenstrual age found no statistically significant differences in rates of bronchopulmonary dysplasia between inhaled nitric oxide and control groups. The approach utilized in the MAPPiNO individual patient data meta-analysis did not report on bronchopulmonary dysplasia as a sole outcome variable. Thus, among premature infants who required respiratory support and were surviving at 36 weeks postmenstrual age, current evidence does not support the hypothesis that treatment with inhaled nitric oxide in the neonatal period reduces the occurrence of bronchopulmonary dysplasia.

The composite outcome of “death or bronchopulmonary dysplasia at 36 weeks postmenstrual age” was reported, although not always as a primary outcome, in 11 inhaled nitric oxide randomized controlled trials. Two individual trials found statistically significant reductions in the composite outcome of death or bronchopulmonary dysplasia in the inhaled nitric oxide-treated group. The Johns Hopkins University Evidence-based Practice Center meta-analysis of 11 randomized controlled trials showed a small, statistically significant reduction in the composite variable death or bronchopulmonary dysplasia at 36 weeks postmenstrual age. Exclusion of the one trial with enrollment after 1 week of age did not change the results of the meta-analysis. The MAPPiNO individual patient data meta-analysis of pooled data from 10 trials showed a similarly small effect size for bronchopulmonary dysplasia or death as the Johns Hopkins University Evidence-based Practice Center analysis, but did not achieve statistical significance. The small effect on this composite outcome should be interpreted cautiously.

The Johns Hopkins University Evidence-based Practice Center systematic review of the effect of inhaled nitric oxide on the severity of bronchopulmonary dysplasia in the randomized controlled trials was compromised by the wide variation in bronchopulmonary dysplasia definitions and other study parameters. The Johns Hopkins University Evidence-based Practice Center analysis concluded that insufficient data are available to perform a meta-analysis for any measure of severity due to the lack of uniformity in definitions and study measures used. There is insufficient evidence to support the hypothesis that treatment with inhaled nitric oxide in the neonatal period reduces the severity of bronchopulmonary dysplasia. Two individual trials reported a statistically significant favorable effect of inhaled nitric oxide on pulmonary outcomes reflecting severity of bronchopulmonary dysplasia; rates of hospitalization and respiratory support at 40 and 44 weeks postmenstrual age; and a statistically significant reduction

in the average duration of supplemental oxygen. Although these trials raise intriguing questions, the effects of inhaled nitric oxide on the severity of bronchopulmonary dysplasia have not been adequately studied in subpopulations, a subject addressed in the panel's response to question 4.

The available evidence therefore is insufficient to recommend the routine use of inhaled nitric oxide in clinical care of premature infants <34 weeks gestation requiring respiratory support.

2. Are There Short-Term Risks of Inhaled Nitric Oxide Therapy Among Premature Infants Who Receive Respiratory Support?

Premature infants are at risk for short-term complications, including patent ductus arteriosus, late-onset (>7 days) sepsis, necrotizing enterocolitis, retinopathy of prematurity, pulmonary complications (e.g., air leak, pulmonary hemorrhage), and brain injury (e.g., intraventricular hemorrhage, intraparenchymal hemorrhage, and periventricular leukomalacia). Although these are morbidities seen in premature infants that might be exacerbated by inhaled nitric oxide, there may be other important indicators to evaluate short-term risks. For example, inhaled nitric oxide may lead to accumulation of methemoglobin, formed by the reaction of nitric oxide with hemoglobin.

The Johns Hopkins University Evidence-based Practice Center analyses showed no evidence for an increased risk of patent ductus arteriosus, late-onset sepsis, necrotizing enterocolitis, retinopathy of prematurity, pulmonary complications, or toxic levels of methemoglobin. The MAPPiNO individual patient data meta-analysis also showed no statistically significant difference in the incidence of air leak, pulmonary hemorrhage, or severe retinopathy of prematurity.

The Johns Hopkins University Evidence-based Practice Center systematic evidence review showed no overall difference between inhaled nitric oxide-treated and control infants with respect to severe intraventricular hemorrhage, intraparenchymal hemorrhage, or periventricular leukomalacia.

The updated Cochrane meta-analysis showed no statistically significant effects on brain injury, either severe intraventricular hemorrhage or the combined outcomes of severe intraventricular hemorrhage or periventricular leukomalacia with early routine administration of inhaled nitric oxide. Early rescue administration of inhaled nitric oxide was associated with a nonsignificant trend toward increased severe intraventricular hemorrhage.

The MAPPiNO individual patient data meta-analysis showed a nonsignificant trend toward increased severe neurological events (e.g., intraventricular hemorrhage, intraparenchymal hemorrhage, cystic periventricular leukomalacia) with inhaled nitric oxide treatment.

In summary, there is no evidence that treatment with inhaled nitric oxide either increases or decreases the risk of several short-term complications of prematurity, including patent ductus arteriosus, late-onset sepsis, severe retinopathy of prematurity, and pulmonary complications (e.g., air leaks, pulmonary hemorrhage). The risks for these complications are greatest for the infants born earliest (at 22 to 27 weeks gestation), and the inhaled nitric oxide trials have not reported on these risks stratified by either birth weight or gestational age with the exception of studies described in the panel's response to question 4. Future research should attempt to fill this gap.

In these trials, administration of inhaled nitric oxide at doses up to 20 parts per million did not produce levels of methemoglobin that would be considered toxic in term infants or adults.

Considering all trials together, there is no convincing evidence to support the hypothesis that inhaled nitric oxide administration increases or decreases the risk of periventricular leukomalacia or intraventricular hemorrhage in premature infants ≤ 34 weeks gestation. These studies varied in design, and only three had baseline head sonograms before treatment with inhaled nitric oxide. When head ultrasound studies were obtained, the timing of these studies and the categorization of brain injury were not uniform.

3. Are There Effects of Inhaled Nitric Oxide Therapy on Long-Term Pulmonary and/or Neurodevelopmental Outcomes Among Premature Infants Who Receive Respiratory Support?

Long-Term Pulmonary Outcomes

The Johns Hopkins University Evidence-based Practice Center reported two randomized controlled trials examining long-term pulmonary outcomes. One large study demonstrated a statistically significant decrease in use of lung-related medications and fewer parental reports of respiratory symptoms at 12 months in children receiving inhaled nitric oxide compared with controls; a smaller study found no statistically significant difference in reported use of lung medications or reports of symptoms at 12 months. Neither study found a statistically significant difference in rates of hospitalization for lung problems or wheezing at 12 months. The lack of a difference in hospitalization or wheezing casts doubt on the clinical importance of a difference in medication use between those who received inhaled nitric oxide and the controls.

When the results of the two 12-month pulmonary follow-up studies were combined in a meta-analysis by the Johns Hopkins University Evidence-based Practice Center, the statistically significant decrease in the reported use of pulmonary medications in children who received inhaled nitric oxide remained, because the smaller study did not have an influence on the overall results.

No studies of long-term pulmonary outcome have included available measurements of pulmonary function, gas exchange, or radiologic appearance. An important deficit of these studies was a failure to account for common confounders following discharge from the neonatal intensive care unit known to have substantial effects on the use of pulmonary medications.

The panel concludes, as did the Johns Hopkins University Evidence-based Practice Center, that there is evidence in one trial of an advantage in long-term pulmonary outcome for the use of inhaled nitric oxide, but that this evidence is not strong enough to justify the widespread use of inhaled nitric oxide to prevent long-term pulmonary disease.

Long-Term Neurodevelopmental Outcomes

None of the trials examining long-term neurodevelopmental outcomes in children have convincingly demonstrated a long-term neurodevelopmental effect of inhaled nitric oxide. Individually, none of the trials found a statistically significant difference in the incidence of motor delay between those who had received inhaled nitric oxide and controls. Few individual trials and none of the meta-analyses revealed a statistically significant association between neonatal inhaled nitric oxide treatment and any neurodevelopmental outcome up to 5 years of age. For cerebral palsy, the two trials that did show associations conflicted in the direction of association. There is insufficient evidence to determine whether there is an effect of

inhaled nitric oxide on motor impairment or if it differs by the birth weight of the treated infants. There also were no significant differences between the inhaled nitric oxide and control groups in the proportion of children with visual or hearing impairment.

Studies of long-term neurodevelopment in preterm infants ≤ 34 weeks gestation treated with inhaled nitric oxide have been hampered by variation in measures used to assess neurodevelopmental status and the ages at which outcomes are measured, and by the lack of physiologic, radiologic, functional, or quality-of-life measures used as outcomes. Most studies of long-term effects typically have used overly broad measures of development in the absence of physiologic or anatomic examinations; many also have used the measure at too young an age. While 18 to 24 months is appropriate for detecting cerebral palsy, testing at school age is more appropriate for diagnosing intellectual disability. Newer methods of assessment, including correlated neuroimaging and standardized behavioral testing, should be included in any future assessments of the long-term neurodevelopmental consequences of inhaled nitric oxide.

Long-term studies of pulmonary and neurodevelopmental health following premature birth are logistically challenging and expensive. Funding agencies should support the expense of long-term follow-up, and investigators should provide comprehensive plans for retention of subjects over the life of the trial.

4. Does the Effect of Inhaled Nitric Oxide Therapy on Bronchopulmonary Dysplasia and/or Death or Neurodevelopmental Impairment Vary Across Subpopulations of Premature Infants?

In response to this question, the panel elected to review common clinical variables that may interact with inhaled nitric oxide treatment apart from timing or duration of treatment, which is covered in the panel response to question 5. Analysis of subpopulations is limited by the fact that few trials have identified subgroups, subgrouping results in small sample sizes in each subcategory, and trials are often not powered to detect subgroup differences. In addition, when trials did define subgroups, definitions varied across trials and were usually post hoc.

Based on the Johns Hopkins University Evidence-based Practice Center systematic review, there is insufficient evidence to evaluate whether factors such as sex, gestational age, ethnic group/race, and socioeconomic status were associated with increased benefit or risk from inhaled nitric oxide therapy. There is no information regarding effects of growth restriction, antenatal steroid use, multiple gestation, chorioamnionitis, or other antenatal factors.

The Johns Hopkins University Evidence-based Practice Center systematic review reveals insufficient evidence of decreased incidence of death or bronchopulmonary dysplasia particular to any subgroup of premature infants treated with inhaled nitric oxide. Five studies (representing three independent clinical trials) reported outcomes by birth weight. Two of the three trials demonstrated a significant reduction in the composite outcome of death or bronchopulmonary dysplasia when inhaled nitric oxide was administered to premature infants $\geq 1,000$ grams, but not in those $\leq 1,000$ grams.

This review raises a concern for safety of inhaled nitric oxide in premature infants <1,000 grams. Three studies of infants of this birth weight treated within 48 hours of delivery reported an increased risk of death, severe intraventricular hemorrhage and periventricular leukomalacia, neurodevelopmental impairment, bronchopulmonary dysplasia, and/or oxygen dependence at 1 year of age. However, in another large study that initiated inhaled nitric oxide at 7 days of life, no such safety concerns were noted in this birth-weight category.

Based on the Johns Hopkins University Evidence-based Practice Center systematic review of published studies, there is insufficient evidence of improvement in neurodevelopmental outcomes in any subgroup of premature infants treated with inhaled nitric oxide.

Published trials have shown insufficient evidence of benefit to premature infants with pulmonary hypoplasia or hypertension, likely due to small numbers of such patients and severity of illness. Additional studies in this population will be difficult to accomplish. Therefore, clinical use in this population should be left to clinical discretion.

Based on published data, the panel recommends special caution in studies of early rescue use of inhaled nitric oxide in premature infants <34 weeks gestation weighing <1,000 grams.

5. Does the Effect of Inhaled Nitric Oxide Therapy on Bronchopulmonary Dysplasia and/or Death or Neurodevelopmental Impairment Vary by Timing of Initiation, Mode of Delivery, Dose and Duration, or Concurrent Therapies?

As previously stated in the Introduction, in the trials published to date, three distinct subgroups have been identified by a Cochrane meta-analysis, by timing of initiation, clinical phase, or severity of illness: (1) early (<3 days) routine initiation in preterm infants receiving respiratory support (“early routine”), (2) early (<3 days) initiation in ventilated infants by oxygenation criteria (“early rescue”), and (3) later (>3 days) initiation in infants at high risk of developing bronchopulmonary dysplasia, as defined by persistent need for respiratory support (“later rescue”). There is a clinical and biological rationale for this subdivision of trials. This meta-analysis within the first two subgroups reveals no significant reduction in death, bronchopulmonary dysplasia, or the composite outcome of death or bronchopulmonary dysplasia in the inhaled nitric oxide study groups. However, the later rescue group is predominantly represented by one, large multicenter trial. In this trial, the treatment protocol, designed to test a novel hypothesis, was unique not only in the timing of initiation, but also in dosing and duration. This trial revealed an overall reduction in the composite outcome of death or bronchopulmonary dysplasia and a post hoc finding of greater efficacy when treatment was initiated during the second postnatal week, as compared with the third postnatal week. The method of treatment allocation and statistical analysis of multiples enrolled in the trial made it difficult to integrate this trial’s findings in a conventional meta-analysis. Nevertheless, different statistical approaches to the analysis of multiples did not substantially change the estimate of the effect of inhaled nitric oxide.

The effect of mode of ventilation (conventional versus high frequency) on efficacy and safety of inhaled nitric oxide was evaluated in two trials, in one by prospective randomization and in the other by post hoc analysis. No studies have directly compared delivery by continuous positive airway pressure or nasal cannula versus endotracheal positive pressure ventilation. There is insufficient evidence to determine whether mode of ventilation impacts outcome from inhaled nitric oxide treatment.

None of the trials published to date randomized subjects by dose or treatment duration of inhaled nitric oxide. Despite this limitation, these trials can be subdivided into three broad dosage groups: 5 parts per million, 10 parts per million, and 20 parts per million. In a dose-stratified meta-analysis by the Johns Hopkins University Evidence-based Practice Center, which combined all three treatment initiation subgroups, inhaled nitric oxide therapy in the group that received a maximum dose of 10 parts per million was associated with a statistically significant reduction in the risk of bronchopulmonary dysplasia, but not death, or the composite outcome of death or bronchopulmonary dysplasia. These results do not form a basis for deciding that one dosing regimen was superior, because they were based on post hoc comparisons and there was too much variability among the study designs within each dose group. A more focused examination of dosing and treatment duration within clinically meaningful subgroups is needed.

Little is known about the effect of concurrent therapies on the efficacy and safety of inhaled nitric oxide. Only one trial directly addressed the effect of inhaled nitric oxide with a concurrent therapy, glucocorticoids. Further research is needed to determine the effect of concurrent therapies—such as antenatal and postnatal glucocorticoids, surfactant, vitamin A, indomethacin, and caffeine—on the efficacy and safety of inhaled nitric oxide.

There is no evidence to suggest that variations in these treatment regimen factors (e.g., dose, timing, mode of administration) are harmful in terms of bronchopulmonary dysplasia, death, or neurodevelopmental outcome. The design of future trials comparing treatment regimens should include a longer duration of follow-up to ensure long-term safety.

There is insufficient evidence to conclude that the efficacy of inhaled nitric oxide therapy with respect to bronchopulmonary dysplasia and/or death, or neurodevelopmental impairment, varies by timing of initiation, mode of delivery, dose and duration of therapy, or concurrent therapies. A major limitation is that only one trial reporting these outcomes has randomized infants by treatment subgroups. Regimens vary considerably among the published studies, such that only broad categorizations of timing or dosing are appropriate for meta-analysis. Although the evidence suggests that some treatment regimens may provide greater benefit, further randomized controlled trials designed to address these specific hypotheses must be undertaken. Among the treatment regimen factors examined in randomized controlled trials, timing of initiation, dosing, and treatment duration currently show the most promise for further research.

6. What Are the Future Research Directions Needed to Better Understand the Risks, Benefits, and Alternatives to Nitric Oxide Therapy for Premature Infants Who Receive Respiratory Support?

1. Understanding risks, benefits, and alternatives to inhaled nitric oxide therapy for premature infants requires investigation of inhaled nitric oxide's mechanisms of action through additional basic research in developmentally relevant experimental models. In particular, future animal and model system studies should focus on understanding the respective roles of dosing, delivery, and timing of therapy and of accompanying ventilation strategies, oxygen management, and concurrent therapies that optimize the benefits of inhaled nitric oxide and reduce the risk of adverse short- or long-term effects. A clearer understanding of the pharmacology and toxicology of inhaled nitric oxide in premature infants is needed to identify better markers of its toxicity and short-term risks. In addition, studies that focus on increasing tissue-specific production of endogenous nitric oxide should be considered.
2. Future trials for evaluation of safety and efficacy of inhaled nitric oxide for premature infants should be informed by prior trials, as well as by future studies in premature animals or other model systems. These trials and preclinical studies should examine both short- and long-term pulmonary and neurodevelopmental outcomes and investigate effect-modifying factors (e.g., pharmacokinetic, genetic, racial/ethnic, and disease risk factors).

3. Future randomized trials should be designed to assess variations in the timing, dose, and duration of treatment, to include a placebo control, to ensure a sample size sufficient to detect a significant interaction between gestational age category and treatment arm, and to consider an appropriate developmental window for efficacy and safety. The positive results of one multicenter trial, which was characterized by later timing, higher dose, and longer duration of treatment, require confirmation. Future trials should attempt to quantify the individual effects of each of these treatment-related variables (timing, dose, and duration), ideally by randomizing them separately.
4. Future trials should assess the long-term effects of inhaled nitric oxide treatment. Important safety and efficacy questions require that study subjects be followed to a minimum of school age with standardized assessments of behavior, cognitive ability, neuroanatomy, and neurophysiology.
5. Design of future efficacy and safety trials of inhaled nitric oxide for premature infants should include interdisciplinary teams of experts in high-risk obstetrics, neonatology, pediatric pulmonology, pediatric neurology, neurodevelopmental follow-up, neonatal pharmacology, lung development, brain development, nitric oxide physiology, biostatistics, and clinical trial design, as well as ethicists, nurses, respiratory therapists, and families.
6. Given the large differences in outcomes of death and bronchopulmonary dysplasia among neonatal intensive care units, new strategies should be considered that improve outcomes by reducing neonatal intensive care unit-specific variations in care.

7. In addition to the panel's inhaled nitric oxide research recommendations, future research should pursue promising strategies other than inhaled nitric oxide.
8. Delay between treatment use and assessment of important outcomes creates a barrier to rapid progress in testing potentially effective treatments. Biomarker, neuroimaging, pulmonary function testing, pulmonary imaging, and other techniques with potentially better predictive accuracy should be developed and tested.

Conclusions

1. Taken as a whole, the available evidence does not support use of inhaled nitric oxide in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation who require respiratory support.
2. There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which inhaled nitric oxide may have benefit in infants <34 weeks gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties.
3. Basic research and animal studies have contributed to important understandings of inhaled nitric oxide benefits on lung development and function in infants at high risk of bronchopulmonary dysplasia. These promising results have only partly been realized in clinical trials of inhaled nitric oxide treatment in premature infants. Future research should seek to understand this gap.

4. Predefined subgroup and post hoc analyses of previous trials showing potential benefit of inhaled nitric oxide have generated hypotheses for future research for clinical trials. Prior strategies shown to be ineffective are discouraged unless new evidence emerges. The positive results of one multicenter trial, which was characterized by later timing, higher dose, and longer duration of treatment, require confirmation. Future trials should attempt to quantify the individual effects of each of these treatment-related variables (timing, dose, and duration), ideally by randomizing them separately.
5. Based on assessment of currently available data, hospitals, clinicians, and the pharmaceutical industry should avoid marketing inhaled nitric oxide for premature infants <34 weeks gestation.

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